From the PROCEEDINGS OF THE ROYAL SOCIETY, VOL. 73.

THE SIGNIFICANCE OF THE ZOOLOGICAL DISTRIBUTION, THE NATURE OF THE MITOSES, AND THE TRANSMISSIBILITY OF CANCER.

BY

E. F. BASHFORD, M.D.,

AND

J. A. MURRAY, M.B., B.Sc.

[*From the* PROCEEDINGS OF THE ROYAL SOCIETY, Vol. 73.]

"The Significance of the Zoological Distribution, the Nature of the Mitoses, and the Transmissibility of Cancer."

By E. F. BASHFORD, M.D., and J. A. MURRAY, M.B., B.Sc.

Communicated by Professor J. ROSE BRADFORD, F.R.S. Received January 12,—Read January 21, 1904.

[PLATE 2.]

The object of this communication is to relate some results of the work conducted under the immediate direction of the Executive Committee of the Cancer Research Fund during the past year. We believe that these results will convince others of the important practical assistance which biologists generally can give in the further elucidation of certain problems of cancer which must be settled before preventive and curative measures can be devised. It will also be made evident that the elucidation of cancer is something more than a problem of human pathology.

We shall adduce evidence tending to show that the wide zoological distribution, the character of the mitoses, and the transmissibility of cancer, are nearly related phenomena with a common basis.

The fundamental significance of ascertaining the extent of the zoological distribution of cancer was recognised by the Cancer Research Fund from the first, and determined the prosecution of definite lines of inquiry, not only with the object of eliciting new facts in regard to the zoological distribution itself, but also with the object of discovering cancer in animals well adapted to cytological and experimental observations.

Zoological Distribution.

Within the past year specimens of malignant new growths have accumulated from all the domesticated animals and from many other

vertebrates. The appended List shows the abundance of the material which has thus been examined. The List includes also specimens which we have been privileged to examine through the courtesy of investigators abroad, who, subsequently to the inauguration of the Cancer Research Fund, have published descriptions of malignant tumours in the lower vertebrates. It is noteworthy that such growths have been obtained, not only in domestic animals, but also in animals living in a state of nature: wild mouse, codfish, gurnard.

The clinical, pathological, anatomical, and microscopical characters of these new growths are identical with those found in man in all essential features, although the animals themselves are drawn from the different classes of the vertebrate phylum. A detailed histological description of the various tumours examined will not be attempted here. Only the general significance of the observations in relation to the incidence of cancer in man will be emphasised.

The great diversity of the habitat, food, and conditions of life generally of the forms in which malignant new growths occur relegates such external conditions to a subsidiary *rôle* in determining the incidence of the disease, and shows that the essential factors must be sought in the potentialities which reside in the cells constituting the living body.

The list of specimens, while giving no safe basis of deduction as to the relative incidence of cancer in the different classes of vertebrates, or of the comparative susceptibility of the different sites of the body, is extremely suggestive.

The large number of epitheliomata obtained in the horse and dog indicates very clearly that malignant new growths are recognised according to the ease with which animals can be examined, and the length of time they are kept under observation. In the same way, numerous malignant new growths have been discovered in the internal organs of cows during the inspection at abattoirs.

Stated generally, it may be said that malignant new growths are known to occur chiefly in animals which are habitually examined with care, and are unrecorded in forms which are difficult to examine or do not reach old age in considerable numbers.

The figures are not sufficiently extensive to determine accurately the age incidence of the various types of new growths in different animals, but a relatively higher incidence in old age is apparent.

The Phenomena of Cell-division in Malignant New Growths.

The progressive increase in size of malignant tumours is due to the division and increase in size of their constituent cells. The process of cell-division is usually indirect, mitotic division of the nuclei preceding the division of the protoplasm. The protoplasm division is frequently

omitted, and multi-nucleated cells are formed, and these may subsequently enter on mitosis, giving rise to pluripolar figures. Amitosis or direct nuclear division also occurs, but its full significance has not yet been determined. It is, however, evident that the occurrence of amitosis does not signify degeneration. The amount of chromatin entering into the equatorial plate of the mitoses of malignant new growths had long been recognised as subject to variation (hyperchromatosis, hypochromatosis, of von Hausemann, 1893), but a new light has been thrown on this phenomenon by a paper communicated to the Royal Society on December 10, 1903, by J. B. Farmer, F.R.S., J. E. S. Moore, F.L.S., and C. E. Walker, entitled "Resemblances exhibited between the Cells of Malignant Growths in Man and those of Normal Reproductive Tissues."

These observers found that while the growing margin of carcinomata and sarcomata presented mitoses similar to those found in other tissues in repair and inflammation, certain cells in the deeper layers, after a slight increase in size, entered on mitosis with ring chromosomes similar to those found in the heterotype division of spore mother-cells of plants and spermatocytes of animals, and like these, with chromosomes in number only half that characteristic of the mitoses of somatic cells. Mitoses similar in character to the somatic divisions, but with reduced number of chromosomes, were also seen (homotype), corresponding to the divisions in the sexual generation of plants and the second ripening divisions of animals. From these observations the authors concluded that malignant new growths were virtually reproductive tissue arising in abnormal situations and possessed of an independence and power of growth like that of the testis in the mammalian body.

This striking sequence of characteristic mitoses had been found in all malignant tumours examined, and was absent in those of benign character. We at once determined to communicate with the authors, who with great courtesy afforded us an early opportunity to examine their preparations. It was then decided to determine how far similar phenomena were characteristic of the malignant new growths occurring in animals. The result has been a complete confirmation of Farmer, Moore, and Walker's observations in tumours from the trout (Mr. Gilruth's and Miss Plehn's cases of adeno-carcinoma), the mouse (two cases of adeno-carcinoma, Jensen's epithelioma), and the dog (mixed cell sarcoma, round cell sarcoma, squamous cell carcinoma). In the columnar cell carcinoma of the trout the phenomena were especially distinct, the small number of chromosomes* (24, 12), the striking contrast between the long slender

* The achromatic figure has always been carefully studied as a control to the observations made on the chromatin of the mitosis. When the chromosomes have been counted, this has been done on Sections 5—10 μ thick, mounted in series.

chromosomes of the somatic mitoses, and the rings of the heterotype division, being of diagrammatic clearness. Homotype mitoses occurred, but were very few in number. Mitoses in the stroma are relatively scanty in the tumours at our disposal, but such as have

FIG. 1.—Adeno-carcinoma of Trout. Homotype amphiaster. Reduced number of chromosomes, arranged transversely in spindle, and showing longitudinal splitting.

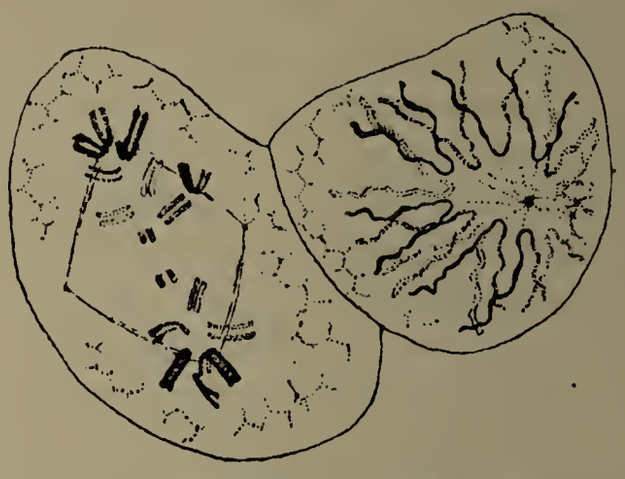


FIG. 2.—Epithelioma of Mouse. Somatic prophase and amphiaster.

FIG. 3.—Epithelioma of Mouse. Heterotype mitosis, late prophase. Ring loop and bivalent chromosomes.

been seen are somatic in character. Farmer, Moore, and Walker record a similar result. In the mouse it has been possible to compare the mitoses in the testis, and those occurring in the irritation produced by iodine, with the result that the significance of the mitoses in cancer has been further confirmed.

The following points are of great importance in these observations. A complicated sequence of cell-changes has been found to be characteristic of carcinoma and sarcoma alike. This sequence is the same as that which initiates the origin of the sexual generation in plants from the asexual, and is terminal in the history of the sexual cells in animals. It must be noted also that all the cells of the malignant new growths do not undergo the reducing division, a certain number differentiate in the direction of the tissue among which they have arisen, and in the secondary growths when present, somatic mitoses occur in the growing margin, which it will subsequently be shown is also a feature in the growth of cancer when transferred to a new host.

FIG. 4.—Heterotype amphiaster, chromosomes arranged longitudinally on spindle. Reduced number. All the chromosomes are not figured.

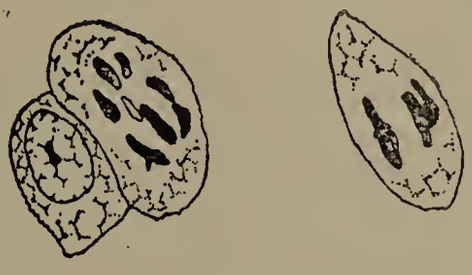


FIG. 5.—Heterotype amphiaster. Ring chromosomes, 12 in number. Adenocarcinoma of Mouse. (The nucleus was contained in two consecutive sections).

The Transmissibility of Malignant New Growths from one Animal to Another.

The transmission of cancer from man to animals, or from one animal to another of different species, has never been successfully performed. Successful transplantation experiments have been made, however, from animals suffering from malignant new growths to others of the same species. The most exhaustive observations in this connection have been made by Jensen and Borrel on mice. Professor C. O. Jensen, of Copenhagen, most generously placed at the disposal of the Cancer Research Fund a portion of one of his experimental tumours,* and with this, and another tumour occurring naturally in a tame mouse, similar experiments have been performed. We have thus been able to confirm Jensen's observations by microscopical examination of the tissues at the site of inoculation at short intervals, and have found that the new tumours which develop arise from the actual cells introduced. While many of these degenerate, a few

* Sent by post under such precautions as to preserve sterility. The transplantations were effected by the Cancer Research Fund five days after the tumour was posted in Copenhagen.

remain of normal appearance, and these gradually increase in number. In the earliest transplantations mitotic division is absent, and it is not till later, when a considerable mass has arisen, that mitoses appear. The earliest mitoses we have been able to observe have been of the somatic type.

Transplantation is, in fact, identical with the process of metastasis as it occurs in the individual providing the tumour. It is remarkable, however, that the tumour of Jensen's experiments does not produce metastases naturally, and its malignancy is only evidenced by its progressive growth, and the undifferentiated character of the cells. The process is in no sense an infection, the tissues of the new host not participating in the formation of the new parenchyma. In this interpretation we are in agreement with Jensen and differ from Borrel, who conceives the results to be due to the agency of a *virus cancéreux*.

The origin of the stroma has not been accurately determined. The power of growth of this tumour is remarkable. In every mouse in which the transplantation succeeds, the new growth may attain a weight equal to that of the animal itself, and over 400 such transmissions have been effected by Jensen in Copenhagen and the Cancer Research Fund in London. A mass of tumour, 16 lbs. in weight, has thus actually arisen from the original one, and that without participation of the cells of the various hosts and without manifest change in structure. This great power of growth is a phenomenon unparalleled in the mammalia, and indicates the potentialities in cases in which widespread dissemination has occurred before death in a human patient.

The experimental transmission of carcinoma shows that we must distinguish between the problem of the genesis of a malignant new growth, and that of the conditions which permit of its continued existence. While the conditions leading to the initiation of malignant tumours are relatively infrequent, we have examined upwards of 1000 tame mice, and have discovered two with cancer; once begun this proliferative activity can, under favourable conditions, persist for a long time unaltered, and can give rise to masses of tissue of great size, having no relation to the restrictions which limit the growth of adult organisms in a large proportion of healthy animals.

The phenomena of cell division, indicating a similarity to the normal reproductive tissues, may help to explain the nature of this great power of multiplication, but leave the problem of cancer genesis practically untouched. They give, however, important indications of the character of the processes on whose elucidation the solution of the question depends. The wide zoological distribution of malignant new growths—its limits are not yet determined—indicates that the cause of cancer is to be sought in a disturbance of those phenomena of

reproduction and cell-life, which are common to the forms in which it occurs.

Our observations on animals show that malignant new growths are always local in origin and of themselves produce no evident constitutional disturbances whatsoever. These facts are in full accord with accumulated clinical experience in man. In connection with diagnosis and statistics we have already emphasised the importance of the absence of specific symptoms. The evidence we have advanced that cancer is an irregular and localised manifestation of a process, otherwise natural to the life-cycle of all organisms, probably explains why it is that malignant new growths and their extensive secondary deposits, *quâ* cancer, are devoid of a specific symptomatology.

We desire to add the accompanying dated note because we find that conclusions which have been drawn by others are attributed to us.

[NOTE.—We find that the guarded terms in which the points of importance are emphasised may lead to a misconception of our interpretation of the facts. The cells which have undergone the reducing division are not responsible for the active invasion of surrounding tissues, nor for the production of metastases; the cells dividing somatically are responsible for both. The number of heterotype mitoses may not stand in any relation to the degree of malignancy, and their absence is only presumptive evidence of the benign character of a tumour. We postulate nothing as to the future of the cells which have undergone the reducing division, though we believe the latter to be a terminal phase in the life cycle of cancer cells as it is in the history of sexual cells in animals. The local origin, and the expansive and infiltrating growth of cancer in its relation to surrounding tissues, while respecting its own proper elements, is the criterion of its malignancy. This stamps it as belonging to a new cycle comparable in its entirety to the whole organism which it is invading, rather than to any one of its tissues, reproductive or otherwise.

We intentionally restricted our original statement to recording the facts, and only such general conclusions as could be irrefutably drawn from them.—*January* 25, 1904].

We cannot here make full acknowledgment to those who have assisted our inquiry in this country, but our indebtedness may be expressed to those observers abroad who have recorded isolated instances of cancer in animals, and have so generously furthered our investigations by placing material or specimens at our disposal.

In particular, we desire to thank Professor Borrel, of the Pasteur Institute; Professor C. O. Jensen, of Copenhagen; Mr. J. A. Gilruth, Chief of the Veterinary Department, New Zealand; Professor Landau and Dr. L. Pick, of Berlin; and Dr. Marianne Plehn, Munich.

Without the generous co-operation of these and many others it would not have been possible within so short a time to have covered the extensive ground indicated in this paper.

Fig. 6.—Homotype amphiaster. Epithelioma Mouse. Transversely arranged chromosomes, longitudinal splitting, reduced number. All the chromosomes are not figured.

List of Specimens of Malignant New Growths examined by the Cancer Research Fund Committee during the year 1903.

Animal.	Age.	Primary site.	Microscopic character.
Cow	Aged	Orbit	Carcinoma, large polygonal cells.
,, ...	,,	Rumen	,, spheroidal cell.
,, ...	,,	,, ...	,, squamous cell.
,, ...	,,	,, ...	,, ,, ,,
,, ...	,,	Liver	,, cubical cell.
,, ...	,,	,, ...	,, ,, ,,
,, ...	,,	? Pleura (secondary)	,, squamous cell.
,, ...	,,	? Gastric gland (secondary)	,, ,, ,,
Heifer	1	Perineum	Melanotic, sarcoma.
Cow	Aged	Ovary	Sarcoma.
,, ...	..	Suprarenal	,,
,, ...	Aged	Ovary	Carcinoma.
,, ...	..	Jaw	Osteo-sarcoma.
,, ...	..	Adrenal	Sarcoma.
,, ...	Aged	Liver	Carcinoma, cubical cell.
,, ...	..	Bowel	Sarcoma, spindle cell.
,, ...	..	Neck	,, ,, ,,
,, ...	Aged	Face and neck .	Carcinoma, squamous cell.
Heifer	2	Side of thigh ..	Melanotic sarcoma.
Dog	14	Mammæ	Carcinoma (scirrhus).
,, ...	10–11	Upper lip	Epithelioma.
,, ...	..	Testis	Sarcoma, mixed cell.
,, ...	..	Upper lip	Fibro-sarcoma.
,, ...	10–11	,, ...	Carcinoma, squamous cell
,, ...	..	Abdominal gland	Sarcoma, round cell.
,, ...	..	Sympathetic glands	Fibro-sarcoma.

List of Specimens of Malignant New Growths—*continued.*

Animal.	Age.	Primary site.	Microscopic character.
Dog	10	Liver	Carcinoma, columnar cell.
,, ...	..	Mouth	,, squamous cell.
,, ...	..	Anus	,, ,, ,,
,, ...	12?	Leg (subcutaneous)	Sarcoma, round cell.
,, ...	..	Sup. max., orbit, gld., l. jaw	,, spindle cell.
,, ...	10	Anal tumour ..	Carcinoma (sebaceous adenoma).
,, ...	11	Spleen, liver, stomach	Sarcoma, spindle cell.
,, ...	12	Leg	,, small round cell.
,, ...	10	Palate, cervical gland	Carcinoma, squamous cell.
,, ...	..	Mammæ	Osteo-sarcoma.
,, ...	10–12	Axilla	Carcinoma, squamous cell.
Horse, gelding ...	10	Penis	Epithelioma.
,, ,, ...	7	,, ...	Carcinoma, squamous cell.
,, stallion ...	15	,, ...	,, ,, ,,
Mare	10	Vulva	,, ,, ,,
Horse	Aged	Lung	,, columnar cell.
,, ...	10	Penis	,, squamous cell.
Mare	14	Vaginal growth	,, ,, ,
Horse	..	Parotid	Medullary carcinoma.
Sheep	2	Mandible	Osteo-sarcoma.
,, ...	..	Liver	Carcinoma, cubical cell.
Pig	..	Sub-max. glands	Sarcoma, mixed cell.
White mouse	..	Inguinal mammæ	Adeno-carcinoma (localised keratinisation).
Yellow mouse	..	Axillary tumour	Adeno-carcinoma.
Wild mouse	..	Mammary glands	Carcinoma, spheroidal cell.
Mouse (Jensen) ..	..	Leg (subcutaneous)	Epithelioma.
,, (Borrell) ..	..	Axilla ,,	Adeno-carcinoma.
,, ,, ..	..	Groin ,,	,,
,, ,, ..	..	,, ,,	,,
,, ,, ..	..	Jaw ,,	Epithelioma.
Mouse (Pick)	..	Back ,,	Adeno-carcinoma (sweat glands).
Cat	10	Tongue	Carcinoma, squamous cell.
Hen (Pick)	..	Floor of mouth	Squamous cell epithelioma.
Indian parakeet ...	..	Pectoral muscle	Myxo-sarcoma.
Giant salamander (Pick).....	..	Testis	Cystic adenoma, malignant.
Cod	..	Air-bladder ...	Sarcoma, spindle cell.
Gurnard	..	Abdominal tumour	Adenoma, malignant.
Trout (Gilruth) ..	..	Floor of mouth	Carcinoma, columnar cell.
,, (Plehn)	..	,, ,,	,, ,, ,,
,, ,, ...	..	,, ,,	,, ,, ,,

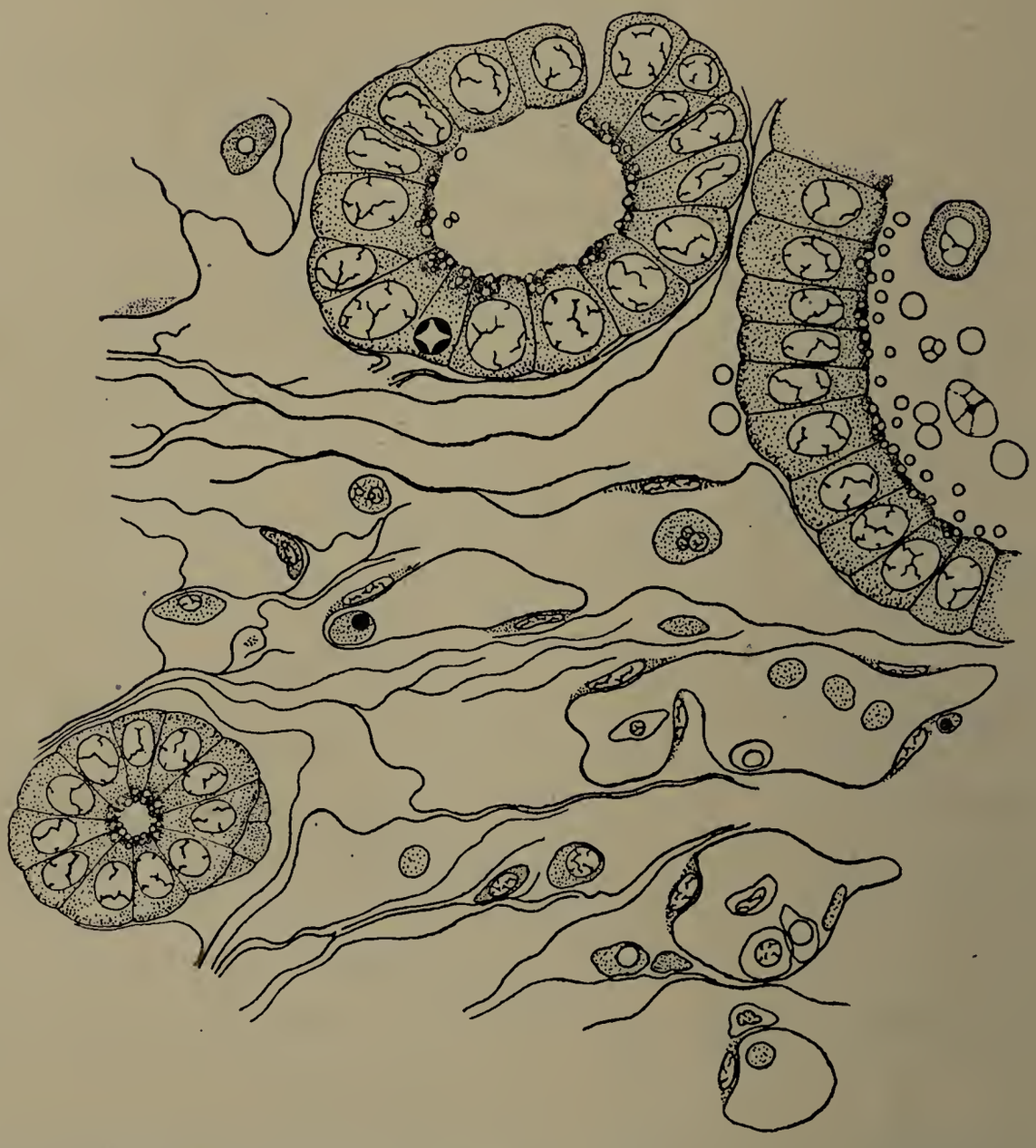
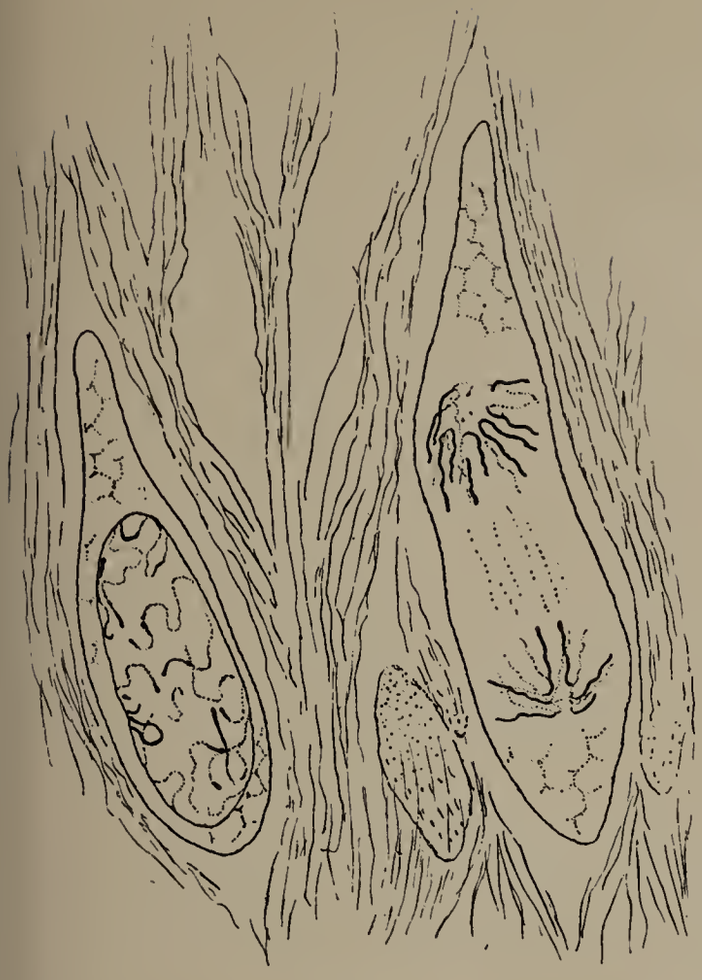
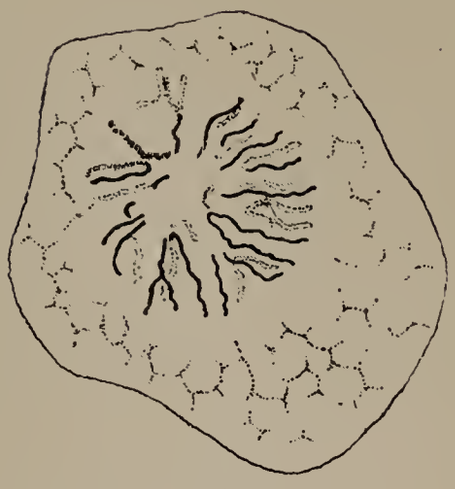


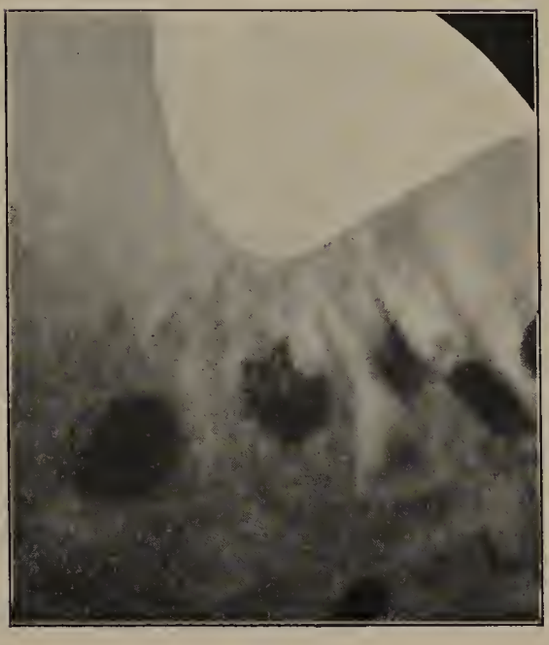
Fig. 7.—Malignant adenoma of Gurnard. Primary tumour. Peritoneal cavity. × 2250 (reduced).



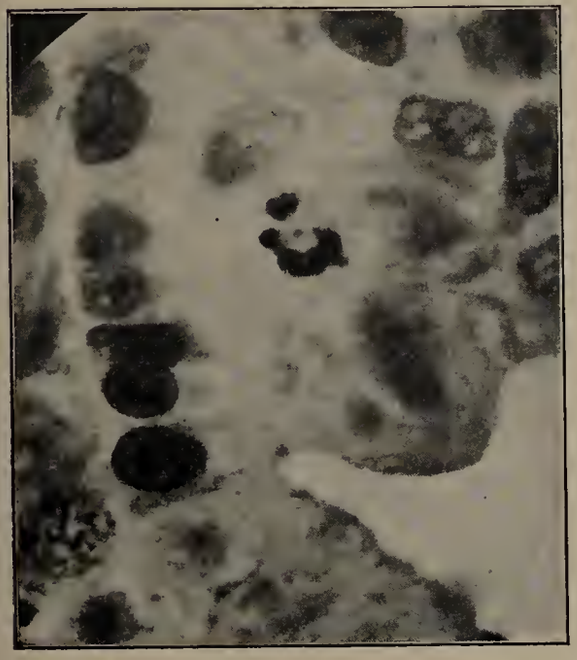
(1)



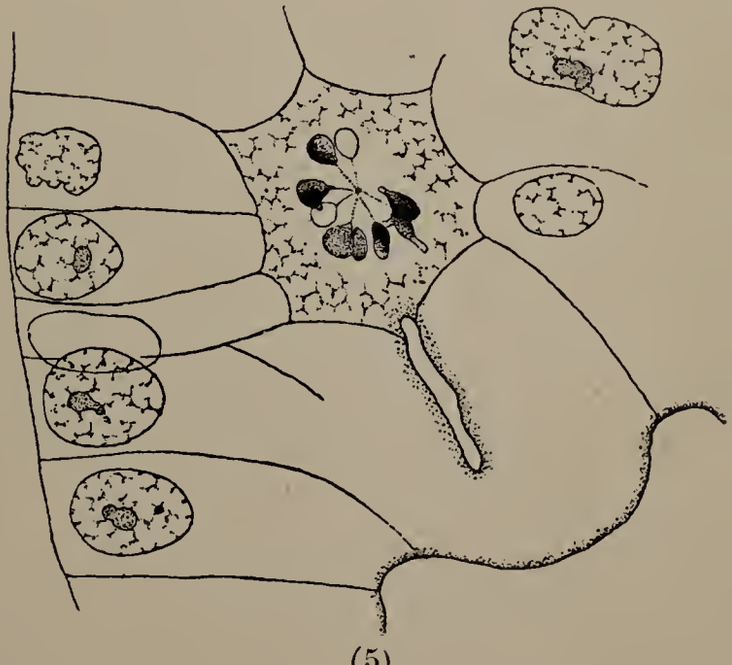
(2)



(3)



(4)



(5)

(6)

FIG. 8.—Spindle cell sarcoma. Codfish. Secondary nodule, wall of swim bladder. × 1500 (reduced).

DESCRIPTION OF PLATE.

ADENO-CARCINOMA OF TROUT.

(1) The chromosomes in the stroma mitoses are long slender V-shaped loops, which split longitudinally, 24 in number. They are somatic in type; compare fig. 2 from the tumour.

(2) Somatic equatorial plate in margin of tumour, seen from the pole, slender V-shaped chromosomes 24 in number arranged transversely on the spindle, and showing longitudinal splitting. All the chromosomes are not reproduced in the figure.

(3) Microphotograph (untouched) of somatic equatorial plate.

(4) Microphotograph (untouched) of heterotype amphiaster seen from pole.

(5) Heterotype amphiaster (polar view). Small ring chromosomes present in reduced number (12). All the chromosomes are not reproduced in the figure. This is a drawing of the mitosis photographed in fig. 4.

(6) Heterotype amphiaster, lateral view (one centrosome only in this section). Ring chromosomes in reduced number arranged longitudinally on the spindle. All the chromosomes are not figured.

HARRISON AND SONS, Printers in Ordinary to His Majesty, St. Martin's Lane.